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Opioid-Induced constipation: Pathophysiology, Treatment and Management

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Abstract

Opioid analgesics are increasingly used to alleviate severe acute and chronic pain. Opioid Induced Constipation (OIC) is the most common side effect of opioid analgesia which can have a significant effect on the persons' quality of life and lead some to decrease or stop taking their analgesia. Although it is recommended that laxative therapy is commenced at the same time as opioid medication, many laxatives do not target the underlying cause of OIC and therefore may be ineffective. As with any patient with constipation other causes should be identified and where possible modified to reduce the risk of OIC. Simple laxatives remain the first line treatment, but there efficacy should be regularly reviewed. Newer opioid antagonist medication should be considered where these are simple laxatives are ineffective.

Key words: Opioid –induced constipation, opioid analgesia, laxatives, constipation, Naloxone, Naloxegol, Methylynaltrexone bromide.

Introduction

Opioids are a major class of analgesics including tramadol, oxycodone and codeine, which are increasingly used to alleviate severe acute and chronic pain, including non-cancer and cancer pain (Moore et al, 2013). Constipation is the most common side effect of opioid analgesia, with between 40-90% of patients developing opioid-induced constipation (OIC) (Coyne et al, 2015). Guidelines therefore state that all patients should commence laxatives at the start of opioid therapy and continue throughout their treatment (National Institute for Health and Care Excellence, (NICE) 2016 and British Medical Association and Royal Pharmaceutical Society, 2016 (March)). Even when this practice is adhered to, around half of patients will not have the desired effect. Most laxatives do not target the underlying cause of OIC, and as such are ineffective. OIC can have a significant impact on quality of life and may provoke some patients to decrease of stop their opioid therapy to relieve the constipation.

Prevalence of Opioid-Induced Constipation

Around one third to one half of the UK population report chronic pain (Fayaz et al, 2016) for which many are prescribed opioid analgesia (Moore et al., 2013). Around half of people admitted into palliative care are reported to experience constipation,

with approximately 80% requiring laxatives, especially those taking opioid medications (Fallon and O'Neill, 1998 and Sykes, 2013). The use of opioid analgesia, frequently results in gastrointestinal side effects, including constipation with estimates of OIC ranging between 40-60% of patients treated with opioid for non-cancer pain, even when laxtive medication is used (Coyne et al, 2015).

Definition of constipation

The term constipation refers to a decrease in the frequency and/or difficulty in passing bowel movements (straining), with the stool typically hard due to the reduced water content (Muller-Lissner and Wald, 2010). Constipation is a symptom not a disease (Blane and Blagrave, 2011). Normal bowel frequency varies, ranging from three bowel movements a day to three per week. Therefore constipation is usually diagnosed when there are fewer than three bowel movements a week (Gray, 2011 and Higgins and Johanson, 2004). Since the mechanism of opioid-induced constipation differs from that of functional constipation (Gaertner et al, 2014), the following consensus definition was proposed by Camilleri et al (2014):
A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following:

- *reduced bowel movement frequency*
- *development or worsening of straining to pass bowel movements*
- *a sense of incomplete rectal evacuation*
- *harder stool consistency*

Neurological control of the bowel

The GI tract is controlled by the autonomic nervous system with sympathetic and parasympathetic nerves working together (Bajwa and Emmanuel, 2009 and Emmanuel, 2004). Sympathetic nerve innervation originates from the superior and inferior mesenteric nerves (spinal cord level T9–T12) and the hypogastric nerve (spinal cord level T11–L2). The hypogastric nerve sends out sympathetic innervation from the L1, L2, and L3 spinal segments to the lower colon, rectum, and sphincter, leading to relaxation of the rectum and anal canal (Emmanuel, 2004 and Bajwa and Emmanuel, 2009). The somatic pudendal nerve (S2–4) innervates the pelvic floor and the external anal sphincter. This nerve stimulates the rectum and anal canal to contract or tighten, causing the internal anal sphincter to relax and allowing faeces to pass through the anus, while the rectum and anal canal contract, assisting in defecation. The internal anal sphincter functions outside of conscious control, meaning that it operates in an automatic manner (Emmanuel, 2004; Bajwa and Emmanuel, 2009). The bowel also has an intrinsic nervous system (known as the enteric nervous system), composed of the submucosal (i.e. Meissner) and myenteric (i.e. Auerbach) plexuses, which largely regulate segment-to-segment movement of the GI tract (Bajwa and Emmanuel, 2009).

How do opioid analgesics cause constipation?

Opioid receptors are an inhibitory group of G-protein-coupled receptors (GPCR) with opioids as ligands that sense molecules outside the cell, activating signal transduction pathways inside the cell which produce cellular responses (Camilleri et al, 2014, Holzer, 2009 and Brock et al, 2012). Both the sympathetic and parasympathetic nervous systems are regulated by GPRC pathways. Centrally opioids antagonize four receptor subtypes: μ (mu), δ (delta), Κ (Kappa) and ORL-1 (opioid receptor-like 1).
Endogenous opioids are dynorhins, enkephalins, endorphins, endomorphins and nociception. In the intestine, met-enkephalin, leu-enkephalin, β-endorphin and dynorphin occur in both neurons and endocrine cells (Camilleri et al, 2014 and Brock et al, 2012).

Many opioids produce their analgesic effect by binding to (μ) mu-opioid receptors in the central nervous system. However they also bind to these receptors peripherally in areas such as the gastrointestinal (GI) tract (Camilleri et al, 2014, Holzer, 2009 and Brock et al, 2012). The GI tract is densely packed with mu-opioid receptors. When released, opioid peptides activate the opioid receptors on the enteric system that controls motility and secretion. OIC is therefore caused by mu-opioid receptor agonists binding to mu-receptors in the myenteric and submucosal plexus (Brock et al, 2012 and Sharma and Jamal, 2013) tissues within the GI tract, this leads to inhibition of the propulsive activity of the intestine and slower gut transit time. Additionally centrally acting opioids may reduce intestinal peristalsis.

The high density of mu (μ) receptors within the enteric system is thought to mediate most of the opioid gastrointestinal side effects including:

- Reducing bowel tone and contractility, which reduces gut transit time.
- Increased pyloric, anal and biliary sphincter tone.
- Reduced enteric, biliary and pancreatic secretions.
- Increased water absorption from the bowel, leading to hard small stool.
- Reduced gastric emptying
- Reduced propulsion of chime through the intestine.

(Camilleri et al, 2014, Holzer, 2009, Brock et al, 2012 and and Sharma and Jamal, 2013)

Assessment

Many patients with constipation will not inform clinicians of their symptoms (Prichard., Norton and Bharucha, 2016). Therefore healthcare practitioners need to pro-actively ask patients receiving opioid medications at each opportunity if they are experiencing any symptoms. The first part of an assessment is to gain an overview of the patient's current bowel habit.
The Rome Foundation (Lacy et al, 2016) suggested the following questions to aid patients describe their bowel habits and to identify bowel dysfunction:

- How frequently do you pass a bowel motion?

- How often are your stools lumpy or hard?
- How often do you have to straining to pass a bowel motion?
- How often do you feel that your bowel motion is incomplete?
- How often do you feel a blockage in your anus when passing a bowel motion?
- How often do you use manual manoeuvres to facilitate a bowel motion?

Adapted from Lacy et al (2016)

In addition to these questions, the Rome III criteria (Mostafa, 2008), is a standardised diagnostic tool for assessing chronic functional constipation. Diagnosis is based on 2 or more of the following symptoms being present for at elaset 12 weeks within the last 6 months:

- Straining at defecation at least 25% of the time
- Emptying stools that are lumpy/hard at least 25% of the time
- Experiencing a sensation of incomplete evacuation at least 25% of the time
- Having three or fewer bowel movements a week.

However the Rome Foundation questions and the Rome III criteria (Mostafa, 2008) were developed for use with the general population and include criteria which are not simple to explain from a patients perspective, and as such may not be adequate for OIC (Ducrotte and Causse, 2012). The Bowel Function Index (BFI) was developed and validated specifically for OIC (Ducrotte and Causse, 2012). The BFI is a clinician administered three item questionnaire that assesses for constipation based on:

- Ease of defecation during the last 7 days according to patient assessment
- Feeling of incomplete evacuation during the last 7 days according to patient assessment
- The patient's judgement of constipation during the last 7 days

The score is expressed as an average between 0-100, with a higher score indicating more severe bowel dysfunction. A score of lower than 28.8 represents normal bowel function, with changes of at least 12 points representing a clinically meaningful difference.

These tools should be used in conjunction with the Bristol stool chart (Heaton and Lewis, 1997) to aid patients describe their stool.

Investigations are required when constipation cannot clearly be linked to opioid use or when OIC does not respond to laxatives (Pritchard., Norton and Bharucha, 2016). Any assessment should consider the patients clinical condition and may include a full blood count and sodium, calcium, potassium and thyroid stimulating hormone levels checked to exclude underlying pathology that can potentially be corrected (Bharucha., Pemberton, and Locke, 2013 and Clark et al, 2012).

Treatment and management options

The primary aim of treatment and management of constipation is to promote a regular, predictable, and comfortable bowel movement for the patient. Any treatment programme should include modification of the person's diet, fluid intake and lifestyle where possible.

Before treating constipation any faecal impaction/loading should be relieved. A combination of oral laxatives and rectal interventions (enemas or suppositories) may be required initially to remove impaction (National Institute for Healthcare Excellence (NICE), 2014a)

Since the effects of different opioids on the gastrointestinal (GI) system vary, for example although codiene, oxycodone and tapentadol can all cause constipation, only codiene leads to delayed colonic transit (Jeong et al, 2012 and Prichard., Norton and Bharucha, 2016). Only 46% of patients treated with opioids report desired treatment results with simple laxatives (Pappagalio, 2001). Therefore opioid antagonists which specifically inhibit the effect of opioids within the GItract may be more effective (Camilleri et al, 2014 and Thomas and Cooney, 2008).Current available opioid antagonists are naloxone (naloxegol), methylnatrexone bromide (British Medical Association and Royal Pharmaceutical Society, 2016 (March)).

A step-wise approach is still advocated utilising simple laxatives as they are inexpensive and can be effective in the management and prevention of OIC (Prichard., Norton and Bharucha, 2016) . A regime should start with regularly administered osmotic agents (e,g, polyethylene glycol such as cosmocol, laxido or movicol), with the addition of a stimulant laxative such as senna on a as- required basis (Prichard., Norton and Bharucha, 2016). Where these are ineffective consideration should be given to commencing either Lubiprostine or Prucalopride (Prichard., Norton and Bharucha, 2016). Lubiprostine and Prucalopride are licensed for the treatment of chronic idiopathic constipation in adults, whose condition has not responded to lifestyle changes (National Institute for Health and Care Excellence (NICE), 2014b). NICE (2014a) define idiopathic chronic constipation as "adults for whom treatment with at least 2 laxatives from different classes, at the highest tolerated doses for at elast 6 months has failed to provide adequate relief and for whom Invasive treatment for constipation is being considered". An inadequate response is defined as opioid-induced constipation symptoms of at least moderate severity in at least 1 of the 4 stool symptom domains (that is, incomplete bowel movement, hard stools, straining or false alarms) while taking at least 1 laxative class for at least 4 days during the prior 2 weeks (NICE, 2014a and NICE, 2010). However, the efficacy of these drugs has not been demonstrated on OIC related cancer pain (Prichard., Norton and Bharucha, 2016).

Prucalopirde

Prucalopride is a selective, high affinity 5-HT_4 receptor agonist, which stimulates colonic mass movement, targeting the impaired motility that is associated with chronic constipation (Kumar., Barker and Emmanuel, 2014).
5-HT_4 receptors (seratonin) are located in the alimentary canal and central nervous

system as well as the urinary bladder, heart and adrenal gland. Serotonin (5-HT) is a chemical that transmits signals to targets within the body and can affect gut motility and sensitivity. Seratonin also triggers reflexes that are crucial for the digestion of food and the elimination of waste products (Mawe and Hoffman, 2012). Prucalopride is an oral medication which is recommended by NICE (2010) for the "symptomatic relief of constipation in women in whom laxatives fail to provide adequate relief". Prucalopride should only be prescribed by clinicians with experience of treating chronic idiopathic constipation and review of the patient's previous laxative treatments.

Lubipostone

Lubiprostone is a ibicyclic fatty acid that activates the chloride channels of the gastrointestinal epithelial cells, producing a chloride rich fluid secretion. Chloride channels are key regulators in the intestinal tract, which transport chloride ions into the lumen with sodium and fluids passively following, thus increasing intestinal fluid secretion (NICE, 2014b). These secretions soften the stool, Increase motility and promote bowel movements (Bajwa and Emmanuel, 2009).

Currently available Opioid antagonists

Naloxone

Naloxone is a centrally and peripherally acting opioid antagonist, the effects of which are predominantly limited to the intestine, due to its high first pass metabolism (Meissner et al, 2000). Naloxone inhibits the stimulation of μ-opioid receptors within the GI tract (Chey et al, 2014). In patients with impaired liver function, the first-pass metabolism of naloxone is reduced and bioavailbility is increased. Naloxone can cross the blood brain barrier which may lead to opioid withdrawal and loss of analgesic effect (Burns., McWilliams and Ross, 2014).

Naloxegol is a form of naloxone which has been pegylated (attached to a molecule of polyethylene glycol, or PEG), therefore reducing its ability to cross the blood-brain barrier (Burns., McWilliams and Ross, 2014 and Camilleri et al, 2014). In this form, it selectively antagonises peripheral opioid receptors to relieve constipation (NICE, 2015).

Methylynaltrexone bromide

Methylynaltrexone bromide is a peripheral selective antagonist of the mu receptor. This is considered peripheral as it is unlikely to cross the blood brain barrier and does not act on the central nervous system. Indicated for opioid induced constipation in terminally ill patients (Camilleri et al, 2014). As methylynaltrexone bromide is only currently available in subcutaneous injection form, some patients may be reluctant to use this option. Methylynaltrexone bromide should only be used where trials of standard laxatives have failed. It has been demonstrated to be less effective for patients who have co-existent modifiable risk factors (Clark et al, 2012).

Conclusion

Constipation is a common symptom for patients taking opioid analgesia, which may prevent adequate pain control. Patients should be proactively asked about symptoms of constipation and laxatives should be provided prophylactically when starting opioid medications in an effort to prevent OIC. As with any patient with constipation other causes should be identified and where possible modified to reduce the risk and impact of OIC. Simple laxatives remain the first line treatment option for patients with OIC however their effectiveness should be regularly reviewed, especially when modifying treatment regimens and increasing analgesic doses. Where newer types of laxatives are required their side effects should be monitored especially in relation to loss of analgesic efficacy.

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